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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/707,737
Filing Date	November 6, 2000
First Named Inventor	Stephen Quake
Group Art Unit	1655
Examiner Name	Arun K. Chakrabarti
Total Number of Pages in This Submission: 1	Attorney Docket Number: 20174C-001810US

ENCLOSURES *(check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm and Individual name	Townsend and Townsend and Crew LLP Hugh Wang Reg. No. 47,163
Signature	
Date	September 13, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this date: September 13, 2002

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FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT | ($) 160

Complete If Known	
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METHOD OF PAYMENT *(check all that apply)*

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☒ Deposit Account:

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fees from below	Fee Paid
Total Claims		-20** =		X		=
Independent Claims		-3** =		X		=
Multiple Dependent				X		=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	160
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) ———————

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($)160

SUBMITTED BY					Complete *(if applicable)*
Name (Print/Type)	Hugh Wang	*Registration No. (Attorney/Agent)*	47,163	*Telephone*	650-326-2400
Signature				*Date*	September 13, 2002

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EWilliams
9.30.02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen Quake et al.

Application No.: 09/707,737

Filed: November 6, 2000

For: Methods And Apparatus For Analyzing Polynucleotide Sequences

Examiner: Arun K. Chakrabarti

Art Unit: 1634

Response To Office Action

Do not Enter
Arun Kr. Chakrabarti
9/30/02

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the "final" Office Action mailed July 3, 2002 in the above-identified application. Reconsideration is respectfully requested in view of the following remarks. A precautionary notice of appeal and the appropriate fees accompany this Response.

Status of the Application and the Present Amendment

Claims 1 to 40 are pending and stand rejected in the application. The claims were rejected as alleged obvious. These rejections, the only issue remaining in the application, is addressed below.

Rejection Under 35 U.S.C. 103

A number of rejections were made in the instant Office Action under 35 U.S.C. 103, alleging that the pending claims are obvious over Livak et al. (U.S. Patent No. 5,945,284) in view of Effenhauser et al. (Analy. Chem. 69:3451-3457), Craighead (U.S. Patent No. 6,214,246), and a few other references. These rejections are respectfully traversed for the reasons stated below.

1. No prima facie obviousness has been or could be established

Applicants respectfully note that the instant Office Action has not provided a prima facie showing of obviousness. As stated in the MPEP (at §§ 706.02(j) and 2143), there are three basic elements that must be met to establish prima facie obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In addition, it must be noted that the suggestion and the reasonable expectation of success must be founded in the prior art, not in Applicant's disclosure. The Court stated that "actual evidence" of a motivation to combine references is required, "[t]hat is, the showing must be clear and particular. *See, e.g., C.R. Bard*, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Id.* [emphasis added] Applicants respectfully submit that the instant Office Action has not fulfilled such requirement.

More significantly, even assuming for the sake of discussion that there is indeed suggestion or motivation to combine the cited art, the combined references do not teach or suggest each and every element of the presently claimed invention. The following details the lack of teaching or suggestion in the cited art of all claim elements of the present invention.

a) Craighead does not teach or suggest multilayer elastomeric material

The Examiner acknowledged that Effenhauser et al. at most showed fabrication of one elastomer layer. The instant rejections are predicated on the Examiner's belief that Craighead teaches multilayer elastomeric material. However, with due respect, such belief is simply incorrect. The Examiner is advised that, unlike the subject invention (e.g., independent claims 1 and 34), Craighead does not teach or suggest microfabricated multilayer elastomeric devices. Rather, the passages cited by the Examiner in Craighead only discussed "multiple sample channels,"

"multiplicity of micron-scale, parallel, spaced pillars," "or "multiple sets of microptic illumination" (see, e.g., the sections noted in the Office Action, the Abstract; Col. 2, lines 28-36; and Col. 3, line 42 to Col. 4, line 11). As explained below, these structures or devices are totally different from the multilayer elastomeric devices of the present invention.

Disclosure of the present invention is not limited to methods utilizing multiple synthesis channels. Rather, the structures employed in the methods (e.g., each synthesis channel) are made with multiple layers of elastomer. These structures are fabricated by bonding multiple (e.g., at least two) layers of elastomer structures, each of which is separately cast, e.g., from a micromachined mold. Detailed discussion of the fabrication procedures is provided in the specification, e.g., at pages 13-17 and figures referenced therein. A simple illustration is shown in Figures 1-4 and accompanying discussion at page 13, line 29 to page 14, line 10. There, a first layer of elastomer is first cast on top of a first mold so to form a first recess in the first layer (Fig. 1). Similarly, a second elastomeric layer is cast on a second mold to form a recess on the second layer (Fig. 2). Thereafter, the second elastomeric layer with the recess is removed from the second mold and placed on top of the first elastomeric layer, thereby forming a flow channel (Fig. 3 and Fig. 4).

By contrast, the microfabrication scheme discussed in Craighead relate to traditional micro-machining methods. Contrary to the assertion of the instant Office Action, it does not disclose microfabrication with multilayer elastomers. First, the "multiple channels" discussed in Craighead simply means that there are more than one channels in the disclosed apparatus. By no means does it suggest or imply that the channels are fabricated with multiple layers of elastomer.

In addition, the "multiplicity of micron-scale, parallel, spaced pillars" discussed in Craighead are also not multilayer elastomers. Instead, they relate to a porous material for separating a sample material as it passes through the sample channels. Craighead stated that:

> the porous material may be an artificial gel structure incorporated in, and fabricated at the same time as, the sample channels. The channels and the gel structure are fabricated by an etching process which produces a very narrow channel and a multiplicity of micron-scale, generally parallel, spaced pillars within this channel and perpendicular to the direction of motion of sample material to be analyzed. [Col. 3, lines 45-52]

From this passage, it is clear that the multiplicity of pillars discussed in Craighead are incorporated in or fabricated at the same time as the sample channels. By no means are they the same as, or even remotely similar to, the multilayer elastomeric structure of the present invention.

Similarly, the "multiple sets of microptic illumination" also bear no resemblance to the multilayer elastomeric fabrication of the present invention. The very description of Craighead makes it abundantly clear that the multiple microptic illumination and multiple channels are provided so that "the structure is completely scalable without the need to extend the optical path length for any channel as the number of sample channels increases" (Col. 2, lines 29-32). Clearly, there is no suggestion of multilayer elastomeric fabrication in Craighead.

b) additional claim features not taught in the cited art

With respect to claims 26-28, the Office Action states that Livak et al. teach pretreating the surface of substrate to create surface chemistry that facilitates polynucleotide attachment and sequence analysis. Applicants respectfully disagree. The section of Livak et al. that was cited in the Office Action, Col. 7, line 35 to Col. 8, line 42, does not contain such teachings. Rather, it discussed different materials that can be used as solid phase support, and their possible sizes, shapes, and other characteristics. Livak et al. at most suggested that the solid substrate can include different linking molecules. However, there is no discussion of pretreating the surface of a solid support to create favorable surface chemistry for immobilizing polynucleotides.

Also, contrary to the assertion in the Office Action, there is no discussion in Livak et al. of coating a solid support with a polyelectrolyte multilayer terminated with a polyanion. The section of Livak et al. cited in the Office Action, Col. 8, lines 19-42, only discusses immobilizing primer/template with, e.g., a biotin-avidin linkage. By contrast, in the present invention, creation of surface chemistry on synthesis channels are prior to, and as a separate step, from immobilization of the primer or templates (see, e.g., page 29, lines 7-16). Thus, these elements of claims 26-28 are clearly not disclosed or suggested in Livak et al.

Based on the above clarifications, it is submitted that the references cited by the Examiner do not teach or suggest each and every element of the presently claimed invention. For at least this reason, a prima facie case of obviousness has not been and could not be established.

2. Nonobvious and advantageous features of the present invention

The present invention is nonobvious not only because it was the present inventors who demonstrated for the first time microfabrication of multilayer elastomeric devices for analyzing polynucleotide sequences. Instead, the nonobvious nature of the subject invention is further demonstrated in the technological breakthrough brought about by the present inventors.

The present invention is predicated in part on the employment of microfluidic devices fabricated from multilayer elastomer structures. The elastomer is a two-component addition-cure silicone rubber. Because each layer has an excess of one of the two components, reactive molecules remain at the interface between the layers. Further curing causes the two layers to irreversibly bond. The device thus created is a monolithic three-dimensionally patterned structure composed of entirely of elastomer. As detailed below, such multilayer elastomeric microfluidic devices represent a significant advance in the art (see Unger et al., *Science* 288:113-116, 2000; of record).

Compared to the traditional micro-machining methods, the advantages provided by the microfabricated fluidic devices in accordance with the present invention are numerous. First, the monolithic elastomeric microfluidic devices can be actuated with surprising speed, permits exceptionally low dead volumes (see also the specification, at page 13, lines 2-4). In addition, because different layers (or parts) of the device are usually composed of the same elastomer, interlayer adhesion failures and thermal stress problems are completely avoided. Interlayer adhesion and thermal stress buildup are problems endemic to conventional micromachining. Also, the elastomer is a soft material allowing large deflections with small actuation forces. Further, the monolithic elastomeric microfluidic devices avoid several practical problems affecting flow systems based on electroosmotic flow or dielectrophoresis, such as electrolytic bubble formation around the electrodes and a strong dependence of flow on the composition of the flow medium. Electrolytic bubble formation seriously restricts the use of electroosmotic flow in integrated microfluidic devices.

In summary, all these advantages not achieved prior to the subject invention strongly indicate that the present invention is nonobvious.

3. Analysis of the instant rejections

With the above explanation and remarks in mind, each of the rejections raised in the instant Office Action is addressed below.

Claims 1-11, 13-21, 26-28, and 34-40 are rejected over Livak et al. in view of Effenhauser et al. and Craighead. In response, Applicants note that Livak et al. and Effenhauser et al do not teach or suggest, expressly or implicitly, microfabricated multilayer elastomeric synthesis channels for immobilizing polynucleotides. As clarified above, such deficiency is not remedied by Craighead since the latter also does not teach or suggest multilayer elastomeric fabrication. Therefore, for this reason alone, claims 1-11, 13-21, 26-28, and 34-40 are nonobvious over the cited art.

Claims 1-21, 26-28, and 34-40 are also rejected as allegedly obvious over Livak et al. in view of Effenhauser et al. and Craighead, and further in view of Koster et al. (US Patent 6,225,567). The Office Action states that Koster et al. teach the elastomeric material RTV silicone. In response, Applicants note that Koster et al. may have discussed elastomeric materials. However, this reference does not teach or suggest microfabrication with multilayer elastomer. Rather, multilayer elastomer microfluidic devices were only taught and enabled by the present inventors, e.g., as demonstrated in Unger et al., *supra*. Therefore, Koster et al. do not make up for the lack of teaching of a multilayer elastomeric microfluidic device in Livak et al., Effenhauser et al., and Craighead. Therefore, this rejection also cannot be properly maintained.

The Office Action further makes rejections of the present invention as allegedly obvious, citing a few more references in addition to the above-discussed art. However, Applicants note that none of these additional references, Williams et al. (US Patent 6,232,075), Clark et al. (US Patent 6,242,528), Batz et al. (US Patent 6,225,052), and Liu et al. (US Patent 6,165,694), teach or suggest use of multilayer elastomeric synthesis channel in analyzing polynucleotide sequence. Thus, even assuming that one would be motivated to combine teachings of the cited art, which is denied, the present invention is nonetheless still nonobvious because the combined teachings of the cited references do not teach or suggest each element of the presently claimed invention.

In light of the above explanations and clarifications, Applicants submit that the presently claimed invention is non-obvious over the cited references and respectfully request withdrawal of all the rejections under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Hugh Wang
Reg. No. 47,163

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